CHAPTER X: STUDIES OF ACUPUNCTURE

I was very fortunate to be at the MGH at a time when we had investigators like Ken Kwong and Wu Ming Teng do some of the earlier studies of acupuncture and of course, other groups, Dr. Cho, who you saw in that wonderful Newsweek feature, was also one of the early pioneers.

But the woman that I give the greatest credit to in my own mind and my own education for providing a neurobiological context to begin to understand it was Kathleen Hui. Kathleen, based on her long experience, clinical experience with acupuncture, was beginning to try to understand which neural systems may be diverse enough in their implications and connections, if you will, to provide and provoke such a wide range of response.

And in this, she came up with the hypothesis that the limbic system was a good candidate because indeed, it was connected to many of the critical brain structures that we believe to be associated with the things that we had come to believe that acupuncture was effective for, things like pain modulation or things perhaps like addiction suppression.

What were the common areas? Well, the limbic system was the candidate, the hypothesis that she generated. And within the limbic system, it was her hypothesis that it was the dopaminergic innervation that might be an initial event that may then lead to a cascade of events involving other neurotransmitter systems that may, in turn, lead to this diversity of applications.

So with this kind of basic hypothesis in mind, Kathleen then began to study the limbic system. Of course, it's intimately involved in autonomic functions, endocrine functions, immune functions, mood and memory, it's broadly connected in a fundamental way because of its, if you will, central and ancient location within the brain, incorporating areas of the medulla, the hippocampus, singular cortex and through its dopaminergic projections to many other areas in the brain, in particular the higher order executive areas of the frontal cortex.

Well, in her initial studies, Kathleen was interested to test this hypothesis of whether she would see an active response within the limbic cortex doing a simple

acupuncture manipulation. This is an acute manipulation. She looked at a few different areas, Large Intestine 4 (LI-4), the **hoogle** area, and Stomach 36 were the two that she tested, and did a very, very simple paradigm.

Because indeed, for almost all functional MRI studies, the trick is to compare the brain in an active state against the brain in a controlled state, because the signal changes that we're looking for are very small relative to the baseline signal variations that exist on our images. So we're always having to try to compare one state against another, which is a challenge of the studies and in some ways, an important limitation and we'll talk about that also as we go on.

But here, she did a very simple paradigm, scanning for approximately ten minutes, short periods of time, a few minutes, where the subject had needles that were being manipulated by trained acupuncture at the bore of the magnet and other periods of rest. And in this case, rest meant the needle was in place, but was not actively being stimulated.

Psychophysically, we've begun to characterize this effect and Kathleen, along with Vitali Napadow and Randy Gollub at our lab, has come up with what they think is a consensual psychophysical survey, the so-called "*de qi* index". Because indeed, when you ask subjects what they feel when they go into an acupuncture, you get a wide range of potential responses, things from aching and soreness and pressure sensations, up to dull pain, some report warmth, others report coolness, so we thought it was important to try to characterize this.

What we saw, however, was that the acupuncture sensation, behaviorally, was quite distinct from a simple sensory control where we tapped the needle right over the acupoint so it was equally noticeable, but did not involve placement of the needle in the tissue and manipulation in that particular way.

Now what did we actually see here? We'll show you some results of acupuncture versus that rest and the hoogle area, that's right here in the thumb, I'm told by clinicians one of the more powerful acupoints in the body. Of course one of the first places she wanted to look was within the somatosensory cortex, because indeed, one could feel the needle when it was in place and being manipulated. And exactly as we would expect,

during the periods of manipulation, there was an increase in signal that was locally correspondent to the primary somatosensory cortex, exactly as we would imagine.

And indeed, if you compare the activation with our tactile stimulation control against the acupuncture, you see a very similar activation, somewhat interestingly even greater activation during the tactile stimulation than during the acupuncture, suggesting again that at least the basic biology of primary somatosensory interaction is the same in acupuncture.

But was that the whole story? Well, obviously not, or I wouldn't have been invited to come down and speak to you today. What she found next was both supportive of her basic ideas, but also quite surprising. Because while she did indeed see changes in signal intensity within the deep parts of the brain, these primary limbic areas that she was interested in, here are three such areas: the nucleus accumbens, the amygdala, the hippocampus, again robustly correlated in time with the stimulation of the needle.

What she saw was surprising in the sense that rather than increases in signal, which we saw on the primary sensory cortex, what we saw in these areas was a decrease in signal in this distributed limbic network and a quite significant decrease in signal, signal decreases that, by the way, were not at all matched when the comparable somatosensory control was provided, even though the somatosensory cortex responded at least as much, if not more during the sensory control. So something was unique and different with the acupuncture stimulation outside the primary sensory areas that we didn't see just with tactile stimulation.

In fact, here now I've kind of changed the color code on you and I think I'll use this for the rest of the slides. Blue in this case represents deactivation, the hotter colors, orange and red, are the activations. Here, the sensory control, we can see some small areas of activation now looking broader at the cortical areas. And we see here in these early studies a distributed network of deactivations within cortical areas, as well as in the sub-cortical areas that I showed previously.

The cerebellum was also involved. The cerebellum, of course, is yet another part of neuroscience that we don't understand very much about. It used to be thought to be predominantly involved in motor control. Now we know it has a whole wide range of functions, is intimately involved in cognitive tasks and emotion regulation, as well as

motor control. And indeed, we saw the same phenomena of deactivation during the *de qi* sensation, quite distinct from what we saw during tactile stimulation.

To follow this up, Iris Chen and Bruce Jenkins in our lab, using a variety of the functional imaging techniques, one developed by Bruce Jenkins where we're now looking at blood volume, rather than the so-called bold effect, but she saw similarly that in an animal model with electrical stimulation to the forepaw, in this case of a rat, a distributed area of deactivations, again within a broad network within the brains of these animals, even in this case anesthetized animals.

Now one of the questions that comes up is, "how does this relate both to regular somatosensory stimulus and also pain?" Unfortunately, we had the opportunity to answer this question through the inadvertent administration of pain in some subjects. Even when performed by skilled acupuncturists, rather than this kind of dull, aching *de qi* sensation, some subjects will, on occasion, report sharp pain. And in this particular subject, in one run, they felt *de qi*; in a subsequent run, they reported sharp pain.

So we went back to the data and said, "What were the differences between those two runs?" And quite interestingly, when we looked at the *de qi* sensation in this subject again generally dropping signal. However, a very different story with sharp pain, we now see a broad and distributed increase in signal, even though again, the same physical manipulation of the needle was being performed, much more robust and positive activation in the pain, indeed, than in the sensory control.

Similar findings were also seen in the cerebellum. So, again one reflecting on the ability and the connections between the little brain, if you will, and the big brain, cerebellum and cerebrum, but also this relative inhibition of activity during acupuncture *de qi* increase in signal during pain.

And here's just a summary of what Kathleen was able to demonstrate by integrating across a variety of different studies this distinction between what we know to be a broad network of areas that are activated during noxious stimuli. And interestingly enough, most of those areas, with the exception of the primary somatosensory area, actually seem to be inhibited during acupuncture, certainly giving us some reason to at least speculate as to the potential therapeutic effects of acupuncture in the setting of pain

because of its ability to modulate the same parts of the brain that we see are active during acute pain.

Let me just move on. So taken as a whole, here now we've -- based on Kathleen's continued work, she summed up the data from 43 different subjects and summed up multiple different acupoints -- We see this broad pattern of deactivation, both in primary central limbic areas, as well as in a distributed cortical network that seems to involve the frontal cortex, temporal pole and posterior parietal cortex.

In fact, looking at this picture has recently raised some very interesting questions based on the work of these investigators, Randy Buckner at St. Louis, and based on ideas that were originally promulgated by Marcus Reichel on this so-called default network.

Now what is this default network? Well, as I mentioned before, FMRI is acquired when we compare, say, an activated state, the brain is doing some task, it's looking at something, it's listening to something, it's performing some mental process, against some kind of rest condition. And typically, investigators will subtract the active condition from the rest condition and look for the areas of the brain that increased in signal.

What Randy and his colleagues did, however, was to go back at that data and say, well, what happens when you do the subtraction the other way around? What happens if you ask the question, what's more active when the subjects are at rest, say, just doing a simple fixation, relative to, say, when they're processing words or doing some other cognitive task?

And of course, in any given task, it's a little ambiguous in terms of how to interpret such data, but what they discovered -- and a recent article by Steve Peterson looked at over a dozen different cognitive tasks and this rest versus activation paradigm -- that during the resting condition, there is again a distributed network of regions which seem to be more activated during rest than during the performance of almost any cognitive task. And interestingly enough, again, some of our favorite areas that we had just seen, posterior parietal cortex, temporal pole, frontal cortex.

So the question, of course, then arises, you know, might acupuncture be having its effect on the same default network, the same homeostatic network that the brain naturally

resorts to when it's not performing some attentionally directed task? It's a very interesting hypothesis.

I think they underline neurobiology of the connections between these areas and what functions this default network is serving during so-called rest, in other words the brain really isn't ever at rest, is a very important one. But it turns out that it may, in fact, be very important if we're ultimately going to understand the effects of something like acupuncture. Certainly, I think it's more than just a coincidence in terms of the connection between these.